PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Shinya KUSUDA, et al.

Docket No: Q93855

Appln. No.: 10/572,937

Group Art Unit: 1624

Confirmation No.: 5148

Examiner: Erich A LEESER

Filed: March 22, 2006

For: PHENYLACETIC ACID DERIVATIVE, PROCESS FOR PRODUCING THE SAME, AND USE

DECLARATION UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Hisao Tajima, hereby declare and state:

THAT I am a citizen of Japan;

THAT I have received the degree of a Master of Pharmaceutical Science in 1987 from Kanazawa University;

THAT I have been employed by Ono Pharmaceutical Co., Ltd. since 1987, where I hold a position as Director, with responsibility for PPAR agonist at Pharmacological Research Laboratories of Ono Pharmaceutical Co., Ltd.

I am one of the inventors of the above-identified application and I am familiar with the Office Action issued in the application.

In the Office Action dated March 24, 2008, the claims were rejected under 35 U.S.C. § 103(a) as being unpatentable over Conner et al, WO 2003/072,100 ("WO '100"). The

Examiner's position was that the compounds disclosed by WO '100 have a close structural similarity to the compounds of the present claims as homologues. However, for the reasons below, the compounds of WO 99/46,232 ("WO '232"), which is also cited in the Office Action, are tested for comparison, instead of the compounds of WO '100.

The following experiments were conducted by me or under my control and supervision.

Comparative experiments were conducted which shows that the compounds of the present invention have unexpectedly superior results when compared to the closest prior art compounds. Specifically, the compounds of the present invention having high PPARδ selectivity and cause fewer side effects. The experimental method carried out for obtaining the data below is described in the present specification at pages 60-63.

Among the rings representing ringA in formula (I) in claim 1 in the present application, 4-(trifluoromethyl)piperidin-l-yl and 3,4-dihydro-1H-isoquinolin-2-yl are saturated rings which necessarily include nitrogen, which is different from the compounds in WO '100. In the comparative experiment, the compound of Example 34-11 in the present application and the compound in Example 2-133 in WO '232, which is the most similar compound to the inventive compound of Example 34-11, are used. Based upon a comparison of the results for the inventive compound 34-11 and the inventive compound of Example 33 with the compound of Example 2-133 in WO '232, the data shows that PPARδ increases significantly by changing rings corresponding to ringA from an unsaturated ring to a saturated ring.

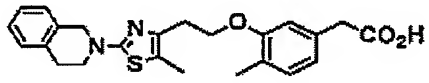
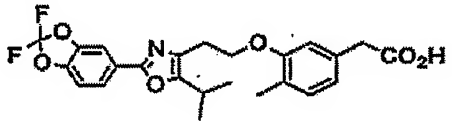
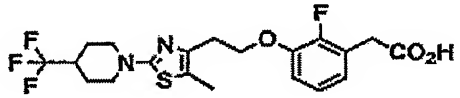
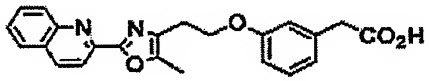
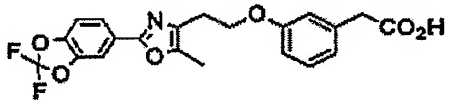
The compound of Example 2-133 of WO '232 was chosen as the comparative compound because when ringA is 2,2-difluoro-1,3-benzodioxol-5-yl in formula (I) of the present application, the compounds of WO '232 are considered to be closer to the present compounds

than the compounds of WO '100. Additionally, in the definition of the substituents of benzene in formula (I) of WO '100 corresponding to ringA in the present claims, although R6 is hydroxy(C 1-C3)alkyl, R7 and R8 are not hydroxy(C1-C3)alkyl. Therefore, benzodioxol can not be formed in the compounds of WO '100. Since benzodioxol can not be formed in the compounds of WO '100, it would not have been expected that PPARδ selectivity increases by changing ring A to be benzodioxol based on the disclosure of WO '100.

Specifically, as described in the "Disclosure of The Invention" section in the present specification, the compound in Example 26 in the present application wherein ringA is 2,2-difluoro-1,3-benzodioxol-5-yl has a structure wherein the combination of each of the substituents, which is not described in WO '232, and the position thereof is preferably selected in order to have selectivity as a PPARδ agonist among three PPAR isoforms: α, γ and δ and to avoid side effects which can occur due to activation of other PPAR isoforms, especially hepatotoxicity. As shown by the comparative experimental data below, the compound in WO '232 (Example 2-96), which is closest to the compound of Example 26 in the present application, has inadequate PPARδ selectivity and inadequate rat PPAR isoforms selectivity. Therefore, the compound of WO '232 (Example 2-96) is not adequate as a pharmaceutical since there is a possibility that the compound has toxicity in safety test in rats.

On the other hand, the compound in Example 26 in the present application has increased selectivity of PPARδ and adequate rat PPAR isoforms selectivity in comparison with the compound of Example 2-96 in WO '232. Thus, the compound in Example 26 in the present application can avoid side effects.

PPAR α, γ, δ agonistic activities

Ex No.	Structure	each human PPAR isoforms agonistic activities (Minimum Effective Concentration (μM)) α	γ	δ	
compound of the present invention					
34-11		30	3	0.01	
26		3	10	<0.01	
33		30	30	0.1	
compounds in WO99/46232 (reference 1)					
2-133		1	10	10	
2-96		1	10	0.01	*inadequate rat PPAR isoforms selectivity

As can be seen from the data above, when ringA in formula (I) of claim 1 of the present application is 4-(trifluoromethyl)piperidin-1-yl and 3,4-dihydro-1H-isoquinolin-2-yl selectivity of PPARδ increases significantly by changing rings corresponding to ringA from an unsaturated ring to a saturated ring. When ringA in formula (I) of the present application is 2,2-difluoro-1,3-benzodioxol-5-yl, the compounds of the invention have has increased selectivity of PPARδ and

adequate rat PPAR isoforms selectivity. In my opinion, one of ordinary skill in the art would not have expected the advantageous effects of the present invention based on the cited references.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: July 15, 2009

Hisao Tajima

HISAO TAJIMA